REMARKS

ANTICIPATION REJECTION

Claims 1-27 stand rejected under 35 U.S.C. § 102(b) as anticipated by Beattie et al. This rejection is respectfully traversed.

The teachings of the Beattie et al. reference differ from the claimed invention in several respects, most of which are associated with the prior art problems that each assay is designed to address.

As explained at paragraph 0009 of the instant application (page 3), prior art competitive hybridization assays suffer from the drawback of requiring bead sets that are unique for each specific variation to be identified, thereby requiring vast amounts of preparation in coupling unique probes to each bead. As explained at paragraph 0021 of the instant application, the present invention overcomes the shortcomings of prior art competitive hybridization assay by providing an assay where the uniquely fluorescent beads containing known capture probe sequences may be adapted for any number of genetic assays since only the differential hybridization probes need to be adjusted without attaching a unique probe to the bead.

Beattie et al. discusses the following problems that the assay described in the patent are designed to address: (i) the spontaneous formation of secondary structure in the single-stranded target nucleic acid (*see*, col. 3, ll. 1-3); (ii) the preparation of isolated single-stranded target DNA to surface-immobilized probes prior to hybridization (col. 3, ll. 38-4); and (iii) the need to label each nucleic acid analyte prior to hybridization to the DNA probe array.

Beattie et al. overcome problems (i), (ii), and (iii) by denaturing and annealing or hybridizing ***unlabeled*** nucleic acid analyte (i.e., the target sequence) with a molar excess of two or more oligonucleotide probes (i.e., the stacking probes) that bind to the target sequence ***in tandem***, forming a duplex region which is stabilized by *uninterrupted contiguous base stacking with the tandemly hybridizing probe*, wherein at least one of the at least two stacking probes is labeled and at least one of the at least two stacking probes may be designed to disrupt interfering secondary structure (col. 7, l. 66, to col. 8, l. 12; Figures 13A and 13B). The signal on the stacking probes is visualized only when the capture probe contiguously hybridizes to the target analyte in tandem with the stacking probes (col. 8, ll. 30-32). Because the target analyte is a denatured double-stranded nucleic acid, the competing reassociation reaction of target strands is minimized by preannealing the denatured target with a molar excess of labeled stacking probes selected to bind to the target on one or both sides of the capture probe (col. 8, ll. 23-28).

The foregoing discussion clearly describes an assay where multiple stacking probes are hybridized contiguously to at least a portion of one strand of a denatured double-stranded analyte and

where *a signal is produced only when the capture probe is hybridized to the target analyte contiguously with the stacking probes.*

Figures 1, 15A and 15B are schematic diagrams of the Beattie et al. assay; these diagrams clearly show that the capture probes of Beattie et al. hybridize to the target nucleic acid analyte and not to the stacking probes and that it is the stacking probes that are labeled and not the target nucleic acid analyte.

Figure 14A(1) shows a situation where the Beattie et al. assay produces a signal as a result of the contiguous hybridization of the capture and stacking probes and Figure 14A(2) shows a situation where the Beattie et al. assay produces no signal because the hybridization of the capture probe is not contiguous with the hybridization of the stacking probes. In Figure 14B, the schematic assay described in this figure will not produce a signal because the analyte has a 10-repeat short tandem repeat polymorphism ("STRP") and the capture and stacking probes are not contiguous throughout the 10-repeat STRP (col. 7, ll. 29-34).

Unlike Beattie et al., the assay of the claimed invention requires the use of ***labeled*** nucleic acid analyte (i.e., the labeled amplicon of claim 1), which is visualized via hybridization of the target analyte to either a wild-type or mutant differential hybridization probe, which is in turn hybridized to a substate-bound capture probe. Figure 3 shows a schematic diagram of the claimed method.

As noted above, the choice of where the label goes is a direct consequence of the problems that the two assays are trying to solve. Thus, with the present invention, by labeling the amplicons and not the differential hybridization probes, the claimed assay is capable of using the same substrate beads for multiple assays by merely changing the differential hybridization probes. By contrast, since Beattie et al. are concerned with the inconvenience of labeling a target sequence, Beattie et al. label the stacking probes. Further, while the present invention individually hybridizes the wild type and differential hybridization probes to individual capture probes in order to bind labeled single-stranded wild type and labeled mutant amplicons, Beattie et al. hybridize labeled tandem stacking probes to the unlabeled denatured double-stranded target analyte to analyze short tandem repeat polymorphisms ("STRP"; Figure 14; col. 7, ll. 14-16), which have a different label for each STRP allele.

The differences between the assay of the claimed invention and the Beattie et al. assay are most evident when Figures 13 to 15 of Beattie et al. are compared against Figure 3 of the instant application. There, the following is clearly seen: (i) that while the present invention labels the *amplicons*, the assay of Beattie et al. labels the *stacking probes*; (ii) that while the present invention generates a signal through the formation of the target analyte-differential hybridization probe-capture probe complex, Beattie et al. generates a signal when the stacking and capture probes are contiguously hybridized to a denatured strand of the labeled analyte.

The foregoing discussion clearly demonstrates that the assay of the present invention is not the same as the assay of Beattie et al. Because the Beattie et al. reference clearly does not anticipate the claimed invention, applicants request withdrawal of this rejection.

CONCLUSION

With this paper, the Examiner's anticipation rejection has been fully addressed and overcome. Because there will be no outstanding issues for this application upon entry of this paper, applicants respectfully request withdrawal of all claim rejections, consideration and rejoinder of withdrawn claims 28-37, and passage of this application to issue.

Any questions regarding this paper or the application in general may be addressed to the undersigned attorney at 650-251-7713 or kcanaan@mintz.com.

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